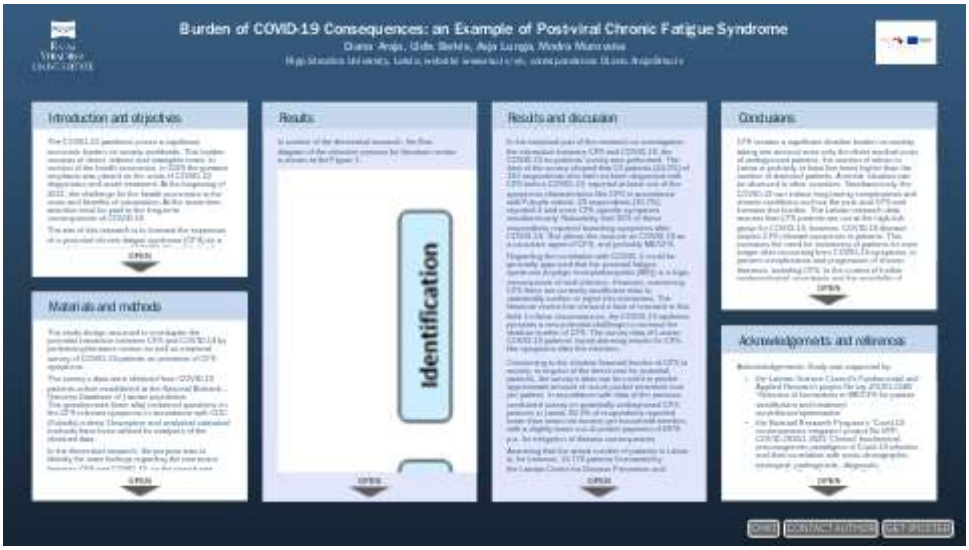
Burden of COVID-19 Consequences: an Example of Post-viral Chronic Fatigue Syndrome



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INTRODUCTION AND OBJECTIVES

The COVID-19 pandemic poses a significant economic burden on society worldwide. This burden consists of direct, indirect and intangible costs. In context of the health economics, in 2020 the greatest emphasis was placed on the costs of COVID-19 diagnostics and acute treatment. At the beginning of 2021, the challenge for the health economics is the costs and benefits of vaccination. At the same time, attention must be paid to the long-term consequences of COVID-19.

The aim of this research is to forecast the expansion of a post-viral chronic fatigue syndrome (CFS) as a potential consequence of COVID-19 and its burden on society.

To achieve the aim of this research the following tasks were defined;

- Conduct a literature review to assess the possible relationship between CFS and COVID-19 and its reflection in scientific publications.

- Test the possible interaction between COVID-19 and CFS in Latvian circumstances, by conducting a survey of COVID-19 patients on presence of CFS symptoms.

- Make preliminary predictions about the potential shadow impact of CFS on society, limiting this study to direct costs to patients.

The discussion section also draws attention to the potential impact of CFS on society in the light of COVID-19.

MATERIALS AND METHODS

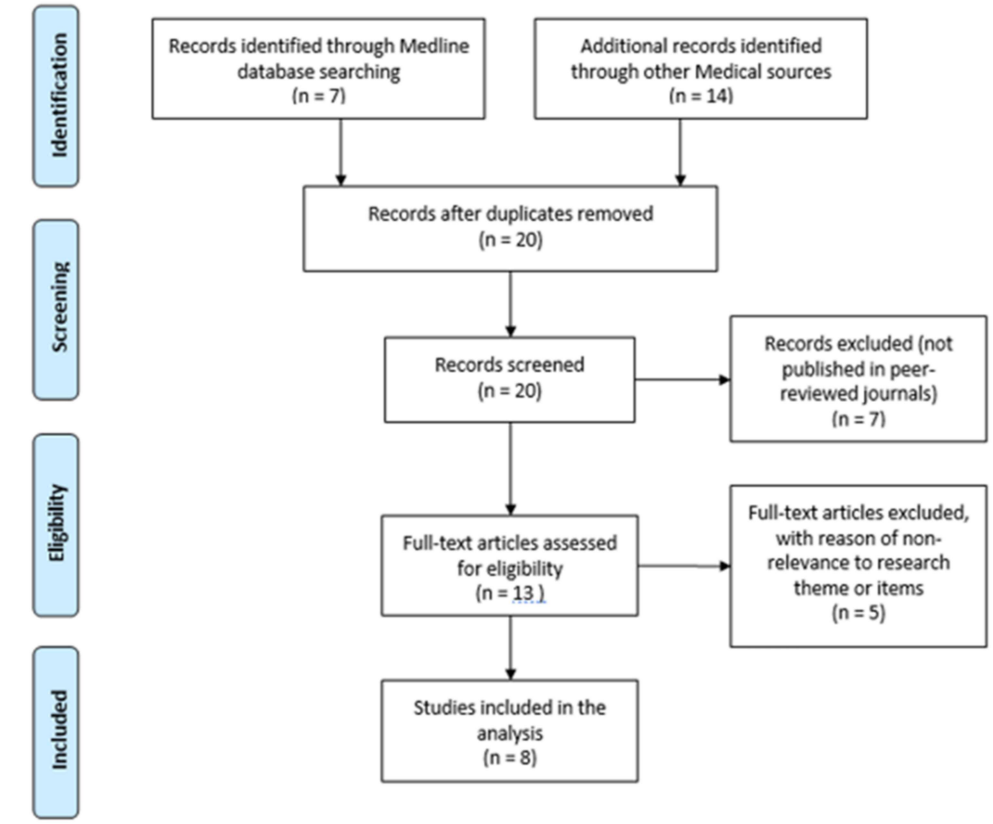
The study design assumed to investigate the potential interaction between CFS and COVID-19 by performing literature review, as well as empirical survey of COVID-19 patients on presence of CFS symptoms.

The survey's data were obtained from COVID-19 patients cohort established at the National Biobank – Genome Database of Latvian population. The questionnaire (inter alia) contained questions on the CFS relevant symptoms in accordance with CDC (Fukuda) criteria. Descriptive and analytical statistical methods have been utilised for analyses of the obtained data.

In the theoretical research, the purpose was to identify the main findings regarding the interaction between CFS and COVID-19, so the search was performed in Medline (via PubMed) and other scientific databases, without publication period restrictions. The following search key words were used in all databases: ('COVID-19') OR ('coronavirus') OR ('SARS-COV-2') AND ('chronic fatigue syndrome') OR ('myalgic encephalomyelitis') OR ('CFS') OR ('ME/CFS'). The flow diagram of the studies selection process is shown at the Figure 1.

RESULTS

In context of the theoretical research, the flow diagram of the selection process for literature review is shown at the Figure 1.



A total of 21 articles were identified using the search strategies (Fig.1). After the removal of duplicates using a reference management software, 20 articles studies were screened for title and abstract, and seven articles were excluded due to unpublished in peer-reviewed journals. The remaining 13 articles were screened against eligibility criteria. Five full-text articles were excluded with reason of non-relevance to research theme or items, and therefore eight articles were included in the analysis.

The main findings of the literature review are presented in a summary of findings table (Table 1). This table provides key information concerning the research authors, type of research, and the sum of available data on the main outcomes.

Table 1. Characteristics of the scientific articles included in analysis to assess the possible interaction between CFS and COVID-19

Authors	Type of research	Main results and conclusions
Strayer *et al*. (Oct 2020) [1]	Research article	The results may have direct relevance to the cognitive impairment and fatigue being experienced by patients clinically recovered from COVID-19 and free of detectable SARS-CoV-2.
Gaber (Jan 2021) [2]	Review	Post-viral fatigue is the most common long-term health issue facing survivors of COVID-19, according to initial reports. Author discusses the risk, diagnosis and principles of management of post-viral fatigue and its chronic variant – ME/CFS – within the context of the pandemic and highlights that further research is urgently needed to guide clinical practice. Several symptoms are classically associated with post-viral fatigue and ME/CFS, including physical pain, recurrent headaches, malaise, cognitive impairment, unrefreshing sleep, recurrent sore throats and lymphadenopathy. These symptoms are strongly associated with the post-exertional phase of the boom-and-bust cycle. Identification of the post-COVID patients needing support and treatment should be a part of the overall COVID-19 response globally.
Friedman *et al.* (Feb 2021) [3]	Opinion	The similarity and overlap of ME/CFS and Longhaul COVID-19 symptoms suggest the similar pathological processes. Unifying hypothesis explains the precipitating events such as viral triggers and other documented exposures: for their overlap in symptoms, ME/CFS and Longhaul COVID-19 should be described as Post Active Phase of Infection Syndromes (PAPIS). Authors further propose that the underlying biochemical pathways and pathophysiological processes of similar symptoms are similar regardless of the initiating trigger. Authors caution that failure to meet the now combined challenges of ME/CFS and Longhaul COVID-19 will impose serious socioeconomic as well as clinical consequences for patients, the families of patients, and society as a whole.
Halpin *et al*. (Feb 2021) [4]	Research article	There is currently very limited information on the nature and prevalence of post-COVID-19 symptoms after hospital discharge. In this research, a purposive sample of 100 survivors discharged from a large University hospital were assessed 4 to 8 weeks after discharge by a multidisciplinary team of rehabilitation professionals. Participants were between 29 and 71 days (mean 48 days) postdischarge from hospital. 32 participants required treatment in intensive care unit (ICU group) and 68 were managed in hospital wards without needing ICU care (ward group). New illness-related fatigue was the most common reported symptom by 72% participants in ICU group and 60.3% in ward group. There was a clinically significant drop in EQ5D in 68.8% in ICU group and in 45.6% in ward group. Authors recommend planning rehabilitation services to manage postdischarge symptoms appropriately and maximize the functional return of COVID-19 survivors.
Simani *et al*. (Feb 2021) [5]	Research article	The obtained data revealed the prevalence of CFS among patients with COVID-19, which is almost similar to CFS prevalence in the general population. Moreover, post-traumatic stress disorder PTSD in patients with COVID-19 is not associated with the increased risk of CFS. This study suggested that medical institutions should pay attention to the psychological consequences of the COVID-19 outbreak.
Townsend *et al*. (Feb 2021) [6]	Research article	The results demonstrate the significant burden of fatigue, symptoms of autonomic dysfunction and anxiety in the aftermath of COVID-19 infection, but reassuringly do not demonstrate pathological findings on autonomic testing.
Graham *et al*. (Mar 2021) [7]	Research article	Non-hospitalized Covid-19 'long haulers' experience prominent and persistent 'brain fog' and fatigue that affect their cognition and quality of life.
Toogood *et al*. (Mar 2021) [8]	Review	Viral infection is an established trigger for the onset of ME/CFS symptoms, raising the possibility of an increase in ME/CFS prevalence resulting from the ongoing COVID-19 pandemic.

The publication period for identified scientific literature was not defined, but the first related publication is dated by October 2020, and more research articles are published in 2021. The Table 1 shows the main research outcomes of published scientific literature in peer-review journals. Notable that the authors pay attention not only to the symptoms, but also to changes in quality of life indicators.

RESULTS AND DISCUSSION

In the empirical part of the research on investigation the interaction between CFS and COVID-19, the COVID-19 ex-patients' survey was performed. The data of the survey showed that 53 patients (44.2%) of 120 respondents who had not been diagnosed with CFS before COVID-19, reported at least one of the symptoms characteristics like CFS in accordance with Fukuda criteria. 20 respondents (16.7%) reported 4 and more CFS specific symptoms simultaneously. Noticeably, that 95% of these respondents reported launching symptoms after COVID-19. This allows the assume on COVID-19 as a causative agent of CFS, and probably ME/CFS.

Regarding the correlation with COVID, it could be generally approved that the postviral fatigue syndrome (myalgic encephalomyelitis (ME)) is a logic consequence of viral infection. However, concerning CFS there are currently insufficient data to statistically confirm or reject this interaction. The literature review has showed a lack of research in this field. In these circumstances, the COVID-19 epidemic presents a new potential challenge to increase the shadow burden of CFS. The survey data of Latvian COVID-19 patients' report alarming results for CFS-like symptoms after this infection.

Concerning to the shadow financial burden of CFS to society, in respect of the direct cost for potential patients, the survey's data can be useful to predict approximate amount of out-of-pocket treatment cost per patient. In accordance with data of the previous conducted survey on potentially undiagnosed CFS patients in Latvia, 66.2% of respondents reported lower than mean net income per household member, with a slightly lower out-of-pocket payment of €979 p.a. for mitigation of disease consequences.

Assuming that the actual number of patients in Latvia is, for instance, 15,770 patients forecasted by the Latvian Centre for Disease Prevention and Control [9] and each of them spend €979 p.a. to reduce the consequences of the disease, the total amount of direct medical cost for undiagnosed patients is more than €15 million p.a. and it may increase by at least 15% under the influence of COVID-19.

CONCLUSIONS

CFS creates a significant shadow burden on society, taking into account even only the direct medical costs of undiagnosed patients, the number of whom in Latvia is probably at least five times higher than the number of detected patients. A similar situation can be observed in other countries. Simultaneously, the COVID-19 can induce long-lasting complications and chronic conditions such as the post-viral CFS and increase this burden. The Latvian research data assume that CFS patients are not at the high-risk group for COVID-19, however, COVID-19 disease causes CFS relevant symptoms in patients. This increases the need for monitoring of patients for even longer after recovering from COVID-19 symptoms, to prevent complications and progression of chronic diseases, including CFS. In the context of further epidemiological uncertainty and the possibility of severe post-viral consequences, preventive measures are becoming significantly important, as well as an integrated diagnostic approach and appropriate treatment could reduce this burden in the future.

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References:

1. Strayer, D.R.; Young, D.; Mitchell, W.M. Effect of disease duration in a randomized Phase III trial of rintatolimod, an immune modulator for Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome. PLoS ONE 2020, 15(10): e0240403. https://doi.org/10.1371/journal.pone.0240403

2. Gaber, T. Assessment and management of post-COVID fatigue. Progress in Neurology and Psychiatry 2021, I Vol. 25 Iss. 1. https://wchh.onlinelibrary.wiley.com/ doi/pdf/10.1002/pnp.698

3. Friedman, K.J.; Murovska, M.; Pheby, D.F.H.; Zalewski, P. Our Evolving Understanding of ME/CFS. Medicina. 2021, 57, 200. https:// doi.org/10.3390/medicina57030200

4. Halpin, S.J.; McIvor, C.; Whyatt, G.; Adams, A.; Harvey, O.; McLean, L.; Walshaw, C.; Kemp, S.; Corrado, J.; Singh, R.; Collins, T.; O'Connor, R.J.; Sivan, M. Postdischarge symptoms and rehabilitation needs in survivors of COVID-19 infection: A cross-sectional evaluation. J Med Virol. 2021, 93:1013–1022. https://doi.org/10.1002/jmv.26368

5. Simani, L.; Ramezani, M.; Darazam, I.A.; Sagharichi, M.; Aalipour, M.A.; Ghorbani, F.; Pakdaman, H. Prevalence and correlates of chronic fatigue syndrome and post-traumatic stress disorder after the outbreak of the COVID-19. Journal of NeuroVirology, Inc. 2021, https://doi.org/10.1007/s13365-021-00949-1

6. Townsend, L,; Moloney, D.; Finucane, C,; McCarthy, K.; Bergin, C.; Bannan, C.; Kenny, R.-A. Fatigue following COVID-19 infection is not associated with autonomic dysfunction. PLoS ONE 2021, 16(2): e0247280. https://doi.org/10.1371/journal. pone.0247280

7. Graham, E.L.; Clark, J.R.; Orban, Z.S.; Lim, P.H.; Szymanski, A.L.; Taylor, C.; DiBiase, R.M.; Jia, D.T.; Balabanov, R.; Ho, S.U.; Batra, A.; Liotta, E.M.; Koralnik, I.J. Persistent neurologic symptoms and cognitive dysfunction in non-hospitalized Covid-19 'long haulers'. Annals of Clinical and Translational Neurology published by Wiley Periodicals LLC on behalf of American NeurologicalAssociation, 2021. https://doi.org/10.1002/acn3.51350

8. Toogood, P.L.; Clauw, D.J.; Phadke, S.; Hoffman, D. Myalgic encephalomyelitis/ chronic fatigue syndrome (ME/CFS): Where will the drugs come from? Elsevier, Pharmacological Research, 2021, 165; 105465. https://doi.org/10.1016/j.phrs.2021. 105465

9. Pheby, D.F.H.; Araja, D.; Berkis, U.; Brenna, E.; Cullinan, J.; deKorwin. J.-D.; Gitto, L.; Hughes, D.A.; Hunter, R.M.; Trepel, D.; Wang-Steverding X. The development of a consistent Europe-wide approach to investigating the economic impact of myalgic encephalomyelitis (ME/CFS): A report from the European Network on ME/CFS (EUROMENE). Healthcare 2020, 8: 88. https://doi.org/10.3390/healthcare8020088